PEER REVIEW HISTORY

This paper was submitted to the JECH but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Change in prevalence of Chronic Kidney Disease in England over time: comparison of nationally representative cross-sectional surveys from 2003 to 2010
AUTHORS	Aitken, Grant; Roderick, Paul; Fraser, Simon; Mindell, Jenny; O'Donoghue, Donal; Day, Julie; Moon, Graham

VERSION 1 - REVIEW

REVIEWER	Paul Stevens Consultant Nephrologist East Kent University Hospitals NHS Foundation Trust, United Kingdom
REVIEW RETURNED	21-May-2014

GENERAL COMMENTS	Thank you for the opportunity to review this paper. The finding of a reduction in prevalence of GFR <60 ml/min/1.73m2 is perhaps unexpected given the findings from other health economies, more particularly the magnitude of the reduction, and particularly given the relative lack of change in the major risk factors. For me the major issues to address surround selection of patients and estimated GFR methodology. Although subjects in the HSE are chosen to be representative less than half of the subjects in each time period had valid serum creatinine results from which to estimate GFR (42.4% in 2003 and 46.3% in the 2009/10 survey). The selection of these participants (who had serum creatinine estimations) is crucial to the ability to draw any meaningful conclusions. The creatinine assay employed (IDMS traceable enzymatic assay) will not have been standardised prior to 2006 but that is not an issue with this particular assay and should not have materially affected results. It is not appropriate to apply the 2 GFR estimating equation used to people under the age of 16 but the equations have now been validated in all age groups above 18. As the authors will know the NEOERICA study was a single creatinine estimate but QICKD followed the accepted international definition closer and the variance between HSE data and QICKD needs more discussion. I would expect to see some discussion surrounding QOF data returns for CKD which are freely available.

REVIEWER	Chris O'Callaghan University of Oxford, UK
REVIEW RETURNED	13-Jun-2014

GENERAL COMMENTS	This manuscript reports an interesting and carefully conducted study suggesting that the prevalence of CKD in the UK has fallen between 2003 and 2009/2010. This is surprising. Data from the US indicate that the prevalence is rising there and the prevalence of overweight, obesity and diabetes mellitus are rising in both the US and the UK. The study compares data from two time points that are 6-7 years apart and the magnitude of the change is striking for this relatively short time period. The CKD prevalence data is based on serum creatinine measurements and the frequency distribution of the tested populations is shifted to the left for the second time point compared to the first time point. The interpretation of the study rests on this left shift. The concern is that this left shift in the creatinine values may not represent a change in the prevalence of CKD, but rather arise from some other cause. The shift is not associated with an obvious change in the shape of the distribution. The authors rightly discuss this issue in some detail and conclude that there is no reason not to regard the change in creatinine distribution as resulting from a change in the prevalence of CKD in the tested population. Are there any factors that might contribute to a leftward shift that are not or perhaps cannot be excluded? A reduction in creatinine production would also lower creatinine levels. Could dietary changes in cooked meat consumption account for a population shift to the left in creatinine values? This is not easily tested in this study but if there is any relevant data to support or refute this suggestion in the UK population it might be useful for the authors to discuss this. There is a marked rise from 6.2 % to 13.3 % in the use of lipid-lowering drugs which are likely to be almost exclusively statins. Statins do have effects on creatinine and creatinine clearance and can also affect muscle which may alter creatinine levels. Such effects may be at play in this study. In the Heart Protection Study simvastatin reduced the rise in creatinine over time in both diabetic and non-diabetic participants. In the GREACE trial statins were associated with a rise in creatinine clearance (a measure of renal function that is relatively independent of creatinine production). In the SHARP trial lipid lowering therapy in participants not already on dialysis at randomisation reduced the outcome of end stage renal

	disease or a doubling of creatinine with an odds ratio of 0.93, but this was not statistically significant (95% CI 0.86-1.01, p=0.09). A further issue that the authors address is that of the stability of the creatinine in the stored samples over time. The Janus serum bank study which is quoted to support the stability of creatinine over time assessed samples stored for around 25 years and concluded from the population distribution that creatinine was reasonably stable. However, the number of samples in the Janus serum bank study was relatively small and the presumption that the population distribution had not changed over 25 years may not have been valid. Nevertheless, if creatinine was unstable over time then the results of the current sample would be biased towards a lower creatinine in the early sample which is not the case. Great care was taken to generate random population representative samples for the overall study, but could the subset of the study population who had a blood test taken have differed in a confounding manner between the two time points? The second time point does have a significantly higher level of higher education and fewer current smokers. Whether this represents the national shifts in education and smoking or selection bias in the group sampled is unclear and might reasonably be addressed by comparison with other available national scale data. There are also changes in the ethnic distribution of the sampled group, with an extra 1% of 'other' ethnicity and fewer 'white' participants. Although the sample age distributions are similar at both time periods, it is established that the population is ageing, so a meaningful population estimate would require weighting for this effect or appropriate sampling. A problem would arise, for example, if the age distribution in the group that had a blood test was shifted to the left compared to the population itself. In this case, it there were improvements in health coupled with longevity such a study could show a fall in CKD when the total population prevalence was rising because it was common in the very elderly who were undersampled. Care must be taken when using the term CKD as only one creatinine value was studied, but as the authors indicate, regression to the mean would tend to reduce the estimate of CKD rather than increase it if multiple samples were studied for each participant. Ultimately, this is a very thought provoking study that has been carefully conducted and will be of great interest. I strongly support publication.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Paul Stevens

1) Although subjects in the HSE are chosen to be representative less than half of the subjects in each time period had valid serum creatinine results from which to estimate GFR (42.4% in 2003 and 46.3% in the 2009/10 survey). The selection of these participants (who had serum creatinine estimations) is crucial to the ability to draw any meaningful conclusions.

Thank you for noting this. Non-response weighting is applied in all analyses to take account of those individuals who did not provide a blood sample and who therefore did not provide a valid serum creatinine value and hence were not included in the analyses. This 'blood non-response weight' deals with differences in demographics and SES between those with samples in each year, as a subset of whole sample. This weight is obtained by multiplying the interview-non response weight (calculated in comparison with national demographic data) by a further weight for non-response to the nurse visit, which compares those who did and did not have a nurse visit in relation to data obtained at the interview, and then by a further weight comparing those who did and did not provide a blood sample at the nurse visit, using additional information from the interview and nurse visit, as appropriate. Full details of how these weights are obtained provided in the final volume of the HSE report each year. We have included an extra sentence in the paper to emphasise this.

2) The creatinine assay employed (IDMS traceable enzymatic assay) will not have been standardised prior to 2006 but that is not an issue with this particular assay and should not have materially affected results. It is not appropriate to apply the 2 GFR estimating equation used to people under the age of 16 but the equations have now been validated in all age groups above 18.

In all of our analyses, we only calculate CKD prevalence in groupings of individuals that are aged 16 and over. Although there is a small discrepancy that the equations have been validated in age groups above 18, and our sample we also include individuals aged 16 to 17, prevalence of CKD in the youngest age grouping (16-35) was so low that repeating analyses for individuals aged 18+ would make negligible difference.

3) As the authors will know the NEOERICA study was a single creatinine estimate but QICKD followed the accepted international definition closer and the variance between HSE data and QICKD needs more discussion. I would expect to see some discussion surrounding QOF data returns for CKD which are freely available.

Thank you for this feedback. We have now mentioned a statement which emphasised that QJCKD is based on routine testing, whereas the HSE did not. We have also included a statement comparing the HSE prevalence to the QOF data (which was 4.2% for 2010).

Reviewer 2: Chris O'Callaghan

1) The CKD prevalence data is based on serum creatinine measurements and the frequency

distribution of the tested populations is shifted to the left for the second time point compared to the first time point. The interpretation of the study rests on this left shift. The concern is that this left shift in the creatinine values may not represent a change in the prevalence of CKD, but rather arise from some other cause. The shift is not associated with an obvious change in the shape of the distribution. The authors rightly discuss this issue in some detail and conclude that there is no reason not to regard the change in creatinine distribution as resulting from a change in the prevalence of CKD in the tested population. Are there any factors that might contribute to a leftward shift that are not or perhaps cannot be excluded?

We thought through this issue thoroughly and cannot think of any other significant factors which could have led to this leftward shift. In any case, we have introduced a correction factor into our analyses which has altered this distribution (see reviewer point 4).

2) A reduction in creatinine production would also lower creatinine levels. Could dietary changes in cooked meat consumption account for a population shift to the left in creatinine values? This is not easily tested in this study but if there is any relevant data to support or refute this suggestion in the UK population it might be useful for the authors to discuss this.

Having researched this issue and looked at the National Diet and Nutrition Survey, there is evidence of an increase the consumption of meat and meat based products, though overall protein consumption and protein consumption from meat products remains stable. We are only able to compare data from 2001-02 to 2008-10. Whilst it is impossible to directly infer if this has led to the shift in serum creatinine values (unlikely, as we would expect a decrease in consumption to lead to leftward shift), it is certainly worth consideration and we have included a statement on this.

3) There is a marked rise from 6.2 % to 13.3 % in the use of lipid-lowering drugs which are likely to be almost exclusively statins. Statins do have effects on creatinine and creatinine clearance and can also affect muscle which may alter creatinine levels. Such effects may be at play in this study. In the Heart Protection Study simvastatin reduced the rise in creatinine over time in both diabetic and non-diabetic participants. In the GREACE trial statins were associated with a rise in creatinine clearance (a measure of renal function that is relatively independent of creatinine production). In the SHARP trial lipid lowering therapy in participants not already on dialysis at randomisation reduced the outcome of end stage renal disease or a doubling of creatinine with an odds ratio of 0.93, but this was not statistically significant (95% CI 0.86-1.01, p=0.09).

Thank you for pointing these relevant studies out. We have amended our paper to address this issue further. We have also referenced a paper by Fried et al. 2001 showing antilipemic agents improved eGFR in patients with renal disease. It is worth noting that our study is not in people with CHD/CKD and all participants in the GREACE trial had LDL>2.6mmol/l. We also adjusted for lipid lowering drugs in the full model as an extra sensitivity analysis, but found this had no effect.

4) A further issue that the authors address is that of the stability of the creatinine in the stored

samples over time. The Janus serum bank study which is quoted to support the stability of creatinine over time assessed samples stored for around 25 years and concluded from the population distribution that creatinine was reasonably stable. However, the number of samples in the Janus serum bank study was relatively small and the presumption that the population distribution had not changed over 25 years may not have been valid. Nevertheless, if creatinine was unstable over time then the results of the current sample would be biased towards a lower creatinine in the early sample which is not the case.

In order to investigate this issue, Julie Day agreed to reanalyse 100 random HSE samples from 2009. We found that, on average, the mean serum creatinine value increased by 5µmol/L over this 5 year time lag. This has implications for our analyses as the 2003 HSE samples were not tested until 2010, therefore the time lag would cause the 2003 HSE creatinine samples to be artificially high, implying an increased likelihood of higher prevalence of CKD. We decided to investigate this issue more thoroughly and sent an additional 400 samples from the 2009 HSE to be reanalysed. Stratified across quintile, we found that the mean serum creatinine value increased by an average of 4.56µmol/L for the 500 random samples. Taking this into account, we decided to apply a regression equation as a correction factor to the 2003 HSE serum creatinine values (Old = 0.303 + 0.940 *New) and to repeat the analyses. We computed a new GFR based on the corrected serum creatinine values for the 2003 HSE and have rewritten the paper taking this into account. We found that prevalence of CKD has still decreased from 2003 to 2009-10 for both MDRD and CKDEPI equations but the gap has narrowed; prevalence of CKD calculated for the 2003 HSE only decreased from 9.6% (based on the old creatinine value) to 6.7% (based on the new creatinine value) for the MDRD equation; this decreased from 7.6% to 5.7% for the CKDEPI equation.

5) Great care was taken to generate random population representative samples for the overall study, but could the subset of the study population who had a blood test taken have differed in a confounding manner between the two time points? The second time point does have a significantly higher level of higher education and fewer current smokers. Whether this represents the national shifts in education and smoking or selection bias in the group sampled is unclear and might reasonably be addressed by comparison with other available national scale data.

We have compared prevalence of degree-level education, smoking status and age between interviewees who had only an interview, a nurse visit but no blood sample, and a blood sample in the two surveys (%). Within each survey year, smoking prevalence and degree level education were similar between all those interviewed (weighted for interview non-response), those who received a nurse visit (weighted for nurse non-response) and those who had a blood sample (weighted for blood non-response). However, the prevalence of degree-level education had increased by over 5% and prevalence of smoking had fallen by 4-5% between the two periods. We have adjusted for the period change in education and smoking in our modelling. We have added a sentence to the discussion.

2003 2009-10

Int WT Nurse WT Blood WT Int WTNurse WT Blood WT

Qualification
Degree 16.8 17.0 17.6 22.2 22.6 22.5
Below degree 57.3 57.9 58.3 55.7 56.3 57.0
None 25.9 25.1 24.0 22.1 21.1 20.6

Smoking
Current 25.4 25.3 25.2 20.8 20.8 21.0
Ex 24.0 23.9 24.1 24.9 25.0 24.8
Never 50.5 50.7 50.7 54.3 54.2 54.2

Age
16-34 31.1 31.0 31.0 31.3 31.3 30.3
35-54 35.0 35.0 35.7 35.3 35.3 35.2
55-64 14.6 14.5 14.4 14.3 14.3 14.8
65-74 10.4 10.5 10.4 10.4 10.4 10.6
75+ 8.9 8.9 8.5 8.7 8.7 8.7

6) There are also changes in the ethnic distribution of the sampled group, with an extra 1% of 'other' ethnicity and fewer 'white' participants. Although the sample age distributions are similar at both time periods, it is established that the population is ageing, so a meaningful population estimate would require weighting for this effect or appropriate sampling. A problem would arise, for example, if the age distribution in the group that had a blood test was shifted to the left compared to the population itself. In this case, it there were improvements in health coupled with longevity such a study could show a fall in CKD when the total population prevalence was rising because it was common in the very elderly who were undersampled.

The table in the previous comment also shows the age breakdown of those having interviews, nurse visits and blood visits to show the non-response weighting adjusts for this. We agree there was a small increase in non-white ethnicity; prevalence of CKD 3-5 in south Asians and Blacks has been shown to be lower so an increase in non-White groups would lower prevalence (1,2). However we adjust for age and ethnicity in the model, this should take account of changes in ethnic prevalence over time. As our results are nationally representative of the general population, then the age, ethnicity, education, smoking habits, etc will change over time. We also calculated the eGFR for White individuals who never smoked over the two time periods to see if CKD changed due to changes in smoking and ethnicity. Median eGFR was 98.2 for CKDEPI and 88.1 for MDRD in 2003 and median eGFR was 98.1 for CKDEPI and 89.3 for MDRD in 2009/10. Difference between these eGFR values is negligible compared to results we have in Table 2.

7) Care must be taken when using the term CKD as only one creatinine value was studied, but as the authors indicate, regression to the mean would tend to reduce the estimate of CKD rather than increase it if multiple samples were studied for each participant.

We have emphasised this limitation in the discussion.

(1) Dreyer G, Aitken Z, Chesser A, Yaqoob MM. The effect of ethnicity on the prevalence of diabetes and associated kidney disease. QJM 2009; 102:261-269.
(2) Hull S, Dreyer G, Badrick E, Chesser A, Yaqoob MM. The relationship of ethnicity to the prevalence and management of hypertension and associated chronic kidney disease. BMC Nephrology 2011; 12:41.

VERSION 2 – REVIEW

REVIEWER	Chris O'Callaghan University of Oxford, UK
REVIEW RETURNED	

GENERAL COMMENTS	This is a very interesting and well conducted study. The authors have undertaken further analyses that have allowed them to refine and underpin their basic thesis. I strongly recommend publication in its present form.

REVIEWER	Paul Stevens Kent Kidney Care Centre East Kent Hospitals University NHS Foundation Trust
REVIEW RETURNED	05-Sep-2014

GENERAL COMMENTS	There are a couple of typos and grammatical errors that require attention (line 18/19, page of 61; line 7, page 8 of 61; line 50, page 9 of 61; line 12, page 15 of 61